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Review

Exercise and oxidative stress: Potential effects of antioxidant dietary strategies in sports

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ABSTRACT

Free radicals are produced during aerobic cellular metabolism and have key roles as regulatory mediators in signaling processes. Oxidative stress reflects an imbalance between production of reactive oxygen species and an adequate antioxidant defense. This adverse condition may lead to cellular and tissue damage of components, and is involved in different physiopathological states, including aging, exercise, inflammatory, cardiovascular and neurodegenerative diseases, and cancer. In particular, the relationship between exercise and oxidative stress is extremely complex, depending on the mode, intensity, and duration of exercise. Regular moderate training appears beneficial for oxidative stress and health. Conversely, acute exercise leads to increased oxidative stress, although this same stimulus is necessary to allow an up-regulation in endogenous antioxidant defenses (hormesis). Supporting endogenous defenses with additional oral antioxidant supplementation may represent a suitable noninvasive tool for preventing or reducing oxidative stress during training. However, excess of exogenous antioxidants may have detrimental effects on health and performance. Whole foods, rather than capsules, contain antioxidants in natural ratios and proportions, which may act in synergy to optimize the antioxidant effect. Thus, an adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintain an optimal antioxidant status. Antioxidant supplementation may be warranted in particular conditions, when athletes are exposed to high oxidative stress or fail to meet dietary antioxidant requirements. Aim of this review is to discuss the evidence on the relationship between exercise and oxidative stress, and the potential effects of dietary strategies in athletes. The differences between diet and exogenous supplementation as well as available tools to estimate effectiveness of antioxidant intake are also reported. Finally, we advocate the need to adopt an individualized diet for each athlete performing a specific sport or in a specific period of training, clinically supervised with inclusion of blood analysis and physiological tests, in a comprehensive nutritional assessment.

Introduction

Oxidative stress reflects an imbalance between production of reactive oxygen species (ROS) and the ability to detoxify reactive intermediates or to repair the resulting damage by an adequate antioxidant defense. This adverse condition may lead to damage of all cellular components, including proteins, lipids, carbohydrates, and nucleic acids [1]. Oxidative stress is recognized to be involved in many physiological conditions (e.g., aging and exercise) and diseases (including inflammation, cardiovascular and neurodegenerative diseases, and cancer) [1]. In particular, the effect of exercise on redox balance is extremely complex, depending on age, sex, and training level, as well as intensity and duration of exercise. Although regular moderate training appears beneficial for oxidative stress and health, acute and strenuous bouts of aerobic and anaerobic exercise can induce ROS overproduction. Nonetheless, although exercise leads to increased

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oxidative stress, the same exercise stimulus appears necessary to allow an up-regulation in endogenous antioxidant defenses according to the hormesis theory (Fig. 1). Specifically, this hypothesis suggests that the organism's reaction to repeated increases in ROS production via exercise bouts involves adaptive mechanisms. In particular, hormesis elicits an antioxidant up-regulation, a shift toward a more reducing environment, induction of increased stress resistance, ultimately leading to an enhanced life span [2]. Same adaptative responses and the detoxifying function of antioxidant enzymes (superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx], glutathione reductase, glutathione-S-transferase) and nonenzymatic antioxidants (such as vitamins E, A, C; glutathione [GSH]; and uric acid) take part in the prevention of excessive oxidative stress related to performance enhancement, aging prevention, and pathological risk in professional athletes [2].

In recent years, the consumption of supplemental antioxidants in athletes has increased enormously despite the unclear evidence of their benefit. The delicate balance between oxidants and antioxidants may be counterbalanced by an adequate dietary/supplemental antioxidant intake (extrinsic factor). In particular, exogenous supplemental antioxidants have received interest as a noninvasive tool useful in decreasing muscle damage and improving exercise performance and in preventing or reducing oxidative stress, improving life span and performance, and lowering specific risks for pathologic outcomes that strenuous exercise produces in athletes [3,4]. Nonetheless, the revision of available information has evidenced a lack of consistent data regarding exogenous antioxidant supplementation effects on physiological parameters, with most studies reporting no or negative effects on these end points [3,4]. Moreover, some studies suggest adverse effects of antioxidant supplementation on the health and performance of exercise-trained individuals [3,4]. In particular, a too-low oxidative stress status may be detrimental and may blunt positive responses related to hormesis because ROS retain key roles as regulatory mediators in signaling processes essential to the correct functioning of cells. Conversely, high doses of antioxidants may negatively affect important ROS-mediated physiological processes because they may shift from antioxidant capacity to prooxidant effects.

At present, few studies if any approach this topic from a whole food or dietary perspective [5–9]. An adequate intake of vitamins and minerals, and the use of natural foods that are rich in antioxidants (fruits, vegetables, etc.) through a varied and balanced diet rich in fruits, fiber, and vegetables could represent the ideal approach to maintaining the optimal antioxidant status as antioxidants are present in natural ratios and proportions, which may act in synergy to optimize the antioxidant effect. The Mediterranean diet could be a suitable candidate, although data in this field are still scarce. In this review, evidence on the relationship between exercise and oxidative stress and potential effects of dietary strategies in athletes are discussed. The differences between diet and exogenous supplementation as well as available tools to estimate effectiveness of antioxidant intake are also reported.

Available biomarkers to estimate oxidative stress status

The measurement of the oxidative stress in vivo is difficult due to the extreme complexity of the antioxidant/oxidant network and the very short half-life of free radicals [2]. Generally, indirect biomarkers are measured, such as conjugated dienes, hydroperoxides, malondialdehyde, 4-hydroxynonenal, hydrocarbons such as pentane and ethane (in breath), F2-isoprostanes, and oxidized low-density lipoprotein [1,2]. Conversely, total antioxidant capacity [TAC] can be estimated in biological fluids and tissues as a whole, or in its components, including enzymatic (such as CAT, GPx, SOD) and non-enzymatic antioxidants (such as vitamins E, A, C, and GSH and uric acid) [1,2]. Currently, no shared

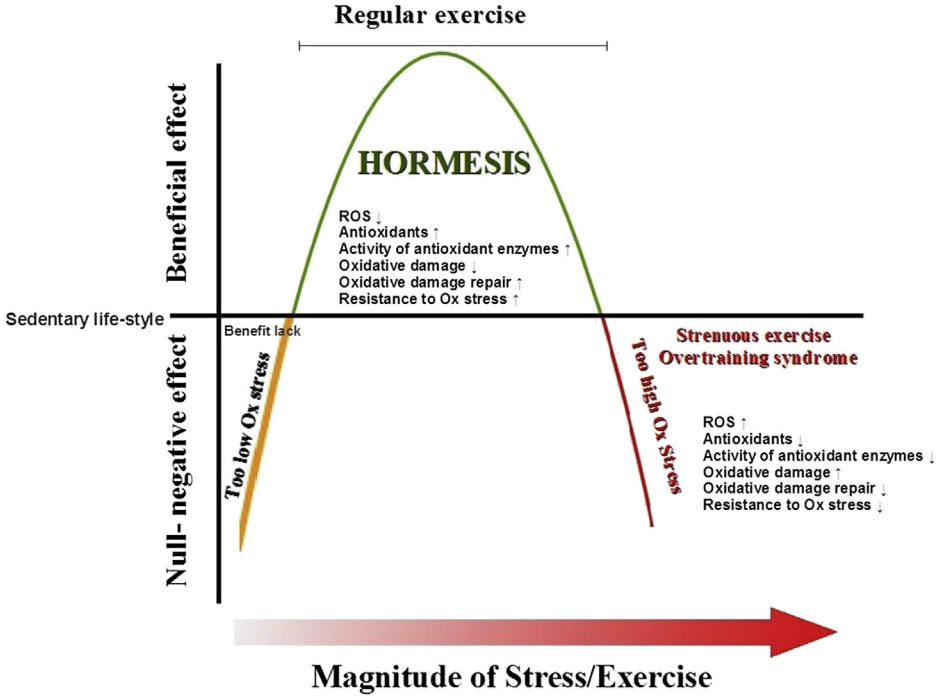

Fig. 1. Hormesis and exercise. Regular exercise elicits hormesis, reduces oxidative stress, protects against disease onset and progression, and improves performance and quality of life. Strenuous exercise and overtraining increases oxidative stress and the risk for diseases. However, an oxidative stress status that is too low leads to a lack of benefits related to hormesis and may be detrimental for health. Ox, oxidative; ROS, reactive oxygen species.

consensus exists on which biomarkers or group of biomarkers must be used to estimate exercise effects as well as bioefficacy of dietary or supplemental antioxidants in sports. Data comparison is still extremely complex for many reasons. They may vary according to presence of different physiological and pathological determinants, including genetic profile, age, sex, lifestyle habits, use of pharmacologic treatments, or concomitant diseases [2]. Some technical aspects such as collection and storage of samples also may have a role in influencing the final results [10]. Time-lagged response may vary according to the biological context evaluated, as DNA changes may be elicited in minutes, whereas variations in erythrocyte enzymes may require days or even weeks.

The choice of specific biomarkers depends on the function affected by the exercise, the effects of the nutrient intake, or both. Conversely, the nature of the parameter used (e.g., enzymatic or nonenzymatic antioxidant, as well as lipoperoxides or protein and DNA oxidation products) may have a great effect on the results obtained.

Effects of exercise on oxidative stress and health

At rest, oxidative stress status is generally found to be lower in athletes than in sedentary individuals, although it also has been observed increased or unchanged [11,12]. Many variables clearly affect these results, two of the most important being differences in experimental design (e.g., exercise intensities) and different methods used to estimate oxidative stress status. Several studies showed a lower oxidative response in athletes than in controls both at rest and soon after exercise, as malondialdehyde (MDA), protein carbonyls, and 8-hydroxydeoxyguanosine were lower in trained athletes compared with untrained individuals, while SOD activity was higher in athletes compared with sedentary individuals [13,14]. Conversely, levels of antioxidant enzymes, such as CAT and GPx, were higher than in sedentary individuals, although these changes were sport-specific and related to the physical status and training level of the athletes [15].

Interestingly, well-trained individuals also may be resistant to sudden oxidative bursts elicited by acute and strenuous exercise, as shown by experimental and human data [16]. Acute exhausting exercise increased erythrocyte MDA in sedentary but not in trained rats, and decreased the erythrocyte SOD activity in sedentary rats, while increasing the activity of this enzyme in trained rats [17]. A recent study showed how levels of oxidative stress appear reduced after an Ironman race [18]. These results are not surprising when seen in view of the so-called hormesis theory, and may also explain the epidemiologic data showing that elite athletes have a longer life expectancy than the general population. In addition, an inverse, linear dose–response relationship was found between volume of physical training and all-cause mortality [2,19,20].

Dietary versus supplemental antioxidants: same effectiveness?

In the past, antioxidant supplementation was expected to be effective against cumulative effects of strenuous exercise–induced free radical damage to heart and skeletal muscle [21]. Vitamin C at various dosages, administered alone or in combination with other antioxidants, chronically or acutely, is the most frequently used antioxidant in human and experimental studies, although with discordant results on its protective role [22]. One of the key determinants for these differences is the dose employed. A vitamin C intake of $\geq$200 mg/d can be reasonably considered “optimal” because it is the amount that achieves near saturation of plasma and full saturation of cells and presumably tissues. A diet including five to nine servings of fruit and raw or steam-cooked vegetables and 200 mL of fresh orange juice could provide the 200-mg vitamin C dose proposed [23]. Male athletes have a range of vitamin C intake of 95 to 520 mg/d, whereas females have intakes ranging from 55 to 230 mg/d, as compared with the Recommended Dietary Allowance of 60 mg/d [24]. However, higher doses of vitamin C can have adverse effects. For instance, a dose $>$1 g/d vitamin C supplementation may reduce mitochondrial biogenesis and ROS generation, as well as reducing beneficial training adaptations and impairing performance [22]. Moreover, 1 g/d (3 times/wk) vitamin C may have prooxidant effects as shown in 23 female athletes under high-intensity training [22]. Additionally, vitamin C administered in doses of 1 g/d ascorbic acid markedly blunted the increase in maximal oxygen uptake (VO_{2max}) in men, in response to an 8-wk exercise program in sedentary men [25]. These adverse vitamin C effects induced by high doses may result from the vitamin’s ability to reduce exercise-induced expression of key transcription factors involved in mitochondrial biogenesis, and prevent the exercise-induced expression of cytochrome C, antioxidant enzymes SOD and GPx [25].

Another important class of antioxidant is represented by polyphenols (including several thousand molecules having a polyphenol structure and classified into different groups depending on their phenol ring number and structural elements that bind these rings to one another) such as quercitin, curcumin, resveratrol, luteolin and cathechin which retain immunomodulatory, antioxidative, antiinflammatory, cardioprotective and anticarcinogenic, and mitochondrial stimulatory activities [26]. In particular, the flavonoids are polyphenols that consist of two aromatic rings bound together by three carbon atoms that form an oxygenated heterocycle, which give color to vegetables, fruits, grains, leaves, flowers. Their effects included the reduction of the activities of the arachidonic acid metabolizing enzymes (phospholipase A2, cyclooxygenase, lipoxygenase), inhibition of proinflammatory cytokines (interleukin [IL]-1 b, IL-2, IL-6, tumor necrosis factor-α), modulation of nitric oxide synthase (NOS) proinflammatory gene expression, and beneficial immunomodulatory effects [27]. Further experimental data suggest that catechin-fed and exercised mice retain higher oxygen consumption, with an increase in skeletal muscle fatty acid β-oxidation [28]. The mRNA levels of mitochondria-related molecules, such as peroxisome proliferator-activated receptor-gamma coactivator-1, cytochrome c oxidase-II, III, and IV in skeletal muscle were also higher in mice given both catechins and exercise [28]. Some studies have shown that organically grown vegetables and fruits may contain higher levels of bioactive molecules, such as polyphenols [29]. Grapes are a source of flavonoids and resveratrol, and organic grape juice intake (300 mL/d for 20 d) may improve glucose homeostasis, antioxidant capacity, and microcirculatory parameters in male elite triathletes [30]. Moreover, levels of insulin and uric acid, functional capillary density, and red blood cell (RBC) velocity increased, whereas glucose levels, erythrocyte SOD activity, and time required to reach RBC velocity during postocclusive-reactive hyperemia decreased after organic grape juice intake [30]. Resveratrol, which shows antiinflammatory properties on adipokine expression and secretion in human adipose tissue in vitro, also induces induce mitochondrial biogenesis [31]. The pharmacologic effects of resveratrol are likely mediated through the activation of sirtuin 1, an enzyme that deacetylates proteins contributing to cellular regulation, including reaction to stressors, longevity, and improvement of insulin sensitivity [32].

Quercetin, a flavonoid contained in many fruits and vegetables, such as tomatoes, blueberries, cherries, onions, and broccoli, at dose of 12.5 or 25 mg/kg (7 d) increased mitochondrial biogenesis in skeletal muscle and brain, and on endurance exercise tolerance in mice [33].

In any case, regardless of whether the antioxidant and anti-inflammatory actions of flavonoids are well reproduced in experimental studies, their potential effects in humans are still unclear [34]. In a recent study, 500 mg quercetin plus 250 mg vitamin C supplementation for 8 wk was effective in reducing oxidative stress and inflammation among young fit and physically active individuals. Moreover, 7 d of quercetin (500 mg twice daily) increased VO_{2max} and endurance capacity in untrained individuals [35]. However, supplementation at higher doses (quercetin 1 g/d) for 3 wk in ultramarathon athletes before a competitive 160-km race did not change levels of inflammatory and oxidative indices [36]. The same study found no change in different indices of immune function after 3 wk of quercetin (1 g/d), but upper respiratory tract infection incidence was reduced in cyclists during the 2-wk period after intensified exercise [37]. A recent meta-analysis also pointed out that although quercetin provides a statistically significant benefit in human endurance exercise capacity (VO_{2max} and endurance exercise performance), the effect remains small, with significant variability between studies [38].

The α-lipoic acid (αLA) supplementation is associated with improvements in skeletal muscle glucose transport activity and whole-body glucose tolerance, and lipid profile [39]. This molecule is effective in affording protection against oxidative stress by the two sulfhydryl moieties [40]. Lipoic acid is unique among antioxidants because it retains powerful antioxidant properties in both its reduced (dihydrolipoic acid) and oxidized (lipoic acid) forms [40]. Both lipoic and dihydrolipoic acids have direct ROS quenching actions as well as metal-chelating ability [40]. Supplementation of αLA (1,200 mg/d for 10 d before exercise) in athletes reduces inflammatory cytokines through changes in thiol redox status [41].

Ubiquinones (coenzyme Q10 [CoQ10]) play an important role as an essential electron carrier in the mitochondrial respiratory chain. The major portion of CoQ10 occurs as ubiquinol-10 in vivo, which plays a role as an antioxidant, in both mitochondria and lipid membranes either by scavenging free radicals directly or in conjunction with α-tocopherol [42]. The daily intake of CoQ10 was estimated to be 3 to 5 mg [43]. Recent data suggests that oral supplementation of CoQ10 during high-intensity exercise reduces oxidative stress and creatinine excretion [44]. Conversely, 8 wk of treatment with a daily CoQ10 dose of 90 mg in moderately trained individuals did not affect exercise capacity and oxidative stress [45].

The ω-3 polyunsaturated fatty acids (PUFAs) are fatty acids that contain more than one double bond in their structure, with effects related to reduce exercise-induced inflammation or oxidative stress and immunomodulatory responses [46,47]. The British Nutrition Foundation (1992) recommended a 3 to 5.5 g daily intake for total ω-3 PUFAs. However, a high daily dose of ω-3 PUFAs in endurance athletes had no effect on exercise performance or inflammation and immunity indices before or after a 3-d period of heavy exertion [46]. Accordingly, a recent literature revision stated that although many data showed the efficacy of ω-3 PUFA supplementation on RBC deformability, muscle damage, inflammation, and metabolism during exercise, few data evaluated the role of ω-3 PUFA supplementation on exercise performance, and available data are still inconclusive [47].

Vitamin E refers to a group of lipid-soluble molecules that include tocopherols and tocotrienols and retains ability to scavenge lipid radicals and terminate oxidative chain reactions [48].

A recent meta-analysis evaluates main data on the use of vitamin E for protection against either exercise-induced lipid peroxidation or muscle damage, although reaching inconclusive result on clear benefit vitamin E supplementation [49].

These data are further complicated by recent experimental findings showing that vitamin E supplementation may be beneficial for animals subjected to acute exercise, although not advisable during training because it prevents or reduces the positive effects of exercise [50].

For vitamin E, as well as for the other antioxidant molecules, available results further demonstrate that a strict definition of some molecules as pro- or antioxidants is somewhat subtle, because antioxidants may become prooxidant both in vivo and in vitro as a consequence of their physical properties and microenvironmental characteristics, as well as to dose and duration in the case of supplementation. Resveratrol may be cited as example for the change between antioxidant and prooxidant effects because at 100 μM, it was able to switch from antioxidant to prooxidant, exacerbating in vitro DNA damage in same samples from runners, depending on the individual basal oxidative stress status [51]. Moreover, other parameters to be considered in the analysis of data pertaining to antioxidant supplementation, which account for the great heterogeneity of data, include type of antioxidant (alone or in combination) and dose and duration time of the treatment. In consideration of these contrasting results, there is no shared agreement in favor of an exogenous antioxidant supplementation [26]. One important reason for the controversy on the use of supplemental antioxidants is the supra-physiological dose reachable by an exogenous intake, which may be detrimental and increase the oxidative stress status (Fig. 2). Moreover, ROS production during exercise is essential to promote the expression of several proteins that are the molecular basis of the exercise-induced hormetic response. Thus, antioxidant supplementation can produce adverse consequences by decreasing the concentration of ROS beyond this required level. For the same reason, if oxidative stress levels are already low, which may be the case with young individuals and athletes, the antioxidant exogenous supplementation may be detrimental (Fig. 2). Furthermore, the additional effects of exogenous supplemental antioxidant on different types of exercise are difficult to predict because exercise itself is a positive stimulus that generally drives antioxidant capacity enhancement (Fig. 3). Moreover, the effects of long-term exogenous antioxidant supplementation on health are also unknown [52].

Nonetheless, antioxidant intake may be beneficial for athletes not consuming a balanced diet. Individuals presenting elevated levels of oxidative stress at a steady state or developing oxidative stress after exhaustive exercise may actually benefit from antioxidant supplementation. It is also important to consider different biological responses related to differences depending on the type of sports (e.g., aerobic versus anaerobic). Additionally, the antioxidant might be effective in particular periods of training (e.g., before or after the race, during overtraining syndrome), and when the requirements may vary according to different seasonal needs. Thus, a personalized plan according to the specific requirement of the athlete during the different phases of training could be the best option, together with the evaluation of the oxidative stress status at rest and its monitoring during training.

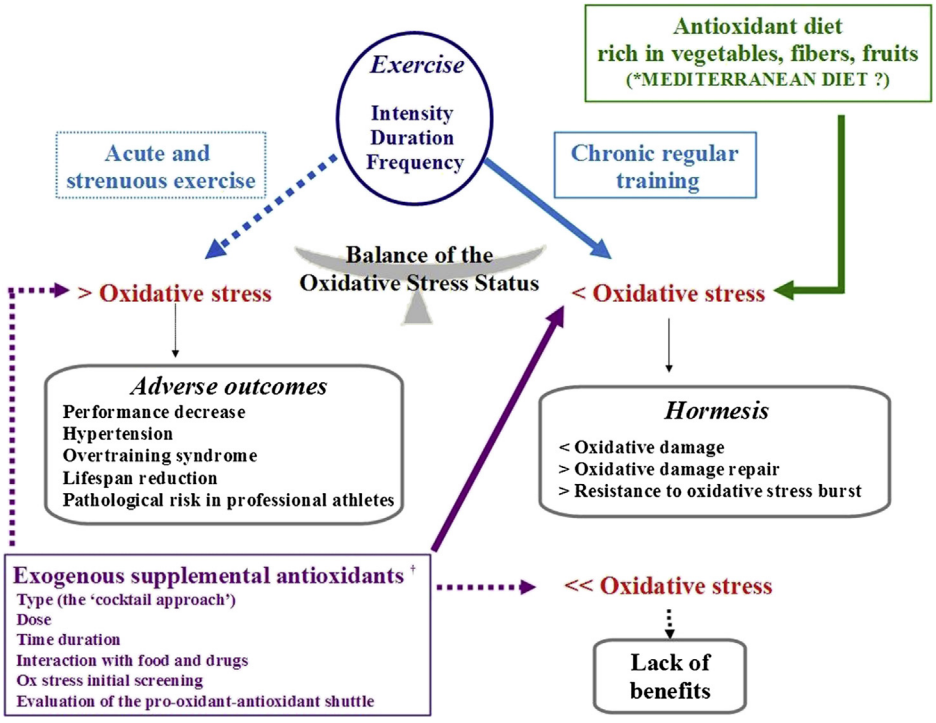

Fig. 2. Integrated effects of exercise (acute and strenuous, and chronic and regular), antioxidant diet (*the Mediterranean diet could be an interesting possibility although more data are needed) and exogenous antioxidant supplementation (†all variables that can be taken in the account of the ratio between benefits and adverse effects) on oxidative stress status and health. The beneficial effects are represented by a solid line, and a dashed line denotes the detrimental effects.

Dietary strategies and oxidative stress in athletes

Most studies concerning the area of recovery from exercise in athletes focus on the use of nutritional supplements rather than on foods [2]. The study of the effects of natural food is difficult because food products are difficult to group according to the type and content of antioxidants. Nonetheless, the protective effect of a diet containing natural sources of antioxidants is probably not equivalent to the protective effect of supplementation. Whole foods, rather than capsules, contain antioxidants in natural ratios and proportions, which may act in synergy to optimize the antioxidant effect. In this context, a diet rich in antioxidants may really be a nonpharmacologic and natural opportunity to maintain a physiological antioxidant status (Fig. 2).

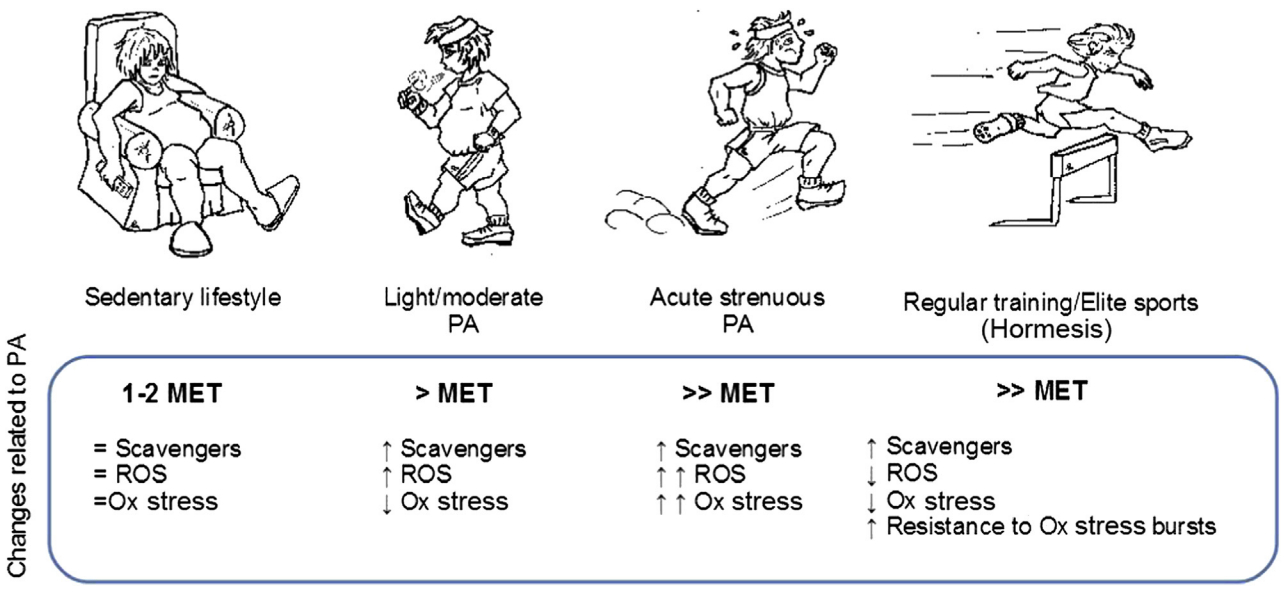

Fig. 3. Effects of physical activity on oxidative stress status. MET, ratio of work metabolic rate to a standard resting metabolic rate; Ox, oxidative; PA, physical activity; ROS, reactive oxygen species.

Evaluating the effects of a unique food without considering its interaction with the more complex and varied combination of nutrients of a complete diet clearly is complex. Moreover, it is also clear that a well-balanced nutritional intake is essential for athletic performance. Many position papers on basic athlete nutrition have been proposed, although a satisfying solution has not yet been reached [53,54]. In fact, nutritional need, as well as quantities of nutrients within food, is strongly influenced by food habits and closely related to country of origin. Moreover, nutrition requirement in athletes is influenced by individual characteristics (sex, age, hormonal changes in women, etc.) in addition to the type of exercise and the training status.

The Mediterranean diet, characterized by high consumption of monounsaturated fatty acids primarily from olives and oil, fruits, vegetables, and whole grains, low consumption of red meat, and a moderate use of red wine, has been found protective for cardiovascular disease and cancer [2,55]. Compared with a high-fat diet, which induces oxidative stress, adherence to the Mediterranean diet enhances antioxidant defenses and improves the lipid profile and low-density lipoprotein oxidation [55–57]. Supplementing a high-fat diet with moderate wine consumption increases plasma antioxidant capacity, decreases oxidative DNA damage, and normalizes endothelial function [56,58]. Adhesion to the Mediterranean diet, combined with moderate to high-intensity endurance training, improves endothelial function in individuals with metabolic syndrome [59]. Specifically, a Mediterranean diet combined with moderate to high-intensity endurance training induced a greater decrease in body weight, insulin sensitivity, and blood pressure, whereas the number of endothelial progenitor cells and cardiorespiratory fitness showed a more marked increase, compared with the improvement of such indices when the Mediterranean diet was adopted alone [59]. Data from the same group also confirmed that adoption of the Mediterranean diet combined with moderate to high-intensity training may lead to greater improvement in quality of life indices and a marked weight loss, with a better physiological response to submaximal effort than adherence to the diet alone [60]. Moreover, adherence to the Mediterranean diet improves muscular mass without increasing total body weight with respect to a protein diet in rugby players [61]. However, available data on the Mediterranean diet are essentially related to aging prevention, and metabolic (of course closely related to sport performance) and degenerative diseases. Thus, more data related to adoption of the Mediterranean diet and its effects in relationship with sports activity in terms of performance enhancement and pathological risk in professional athletes are needed to clearly define possible beneficial effects against exercise-related oxidative stress.

Conclusions

The interrelationship of exercise and oxidative stress remains extremely complex, depending on the mode, intensity, and duration of exercise, and individual susceptibility to oxidative stress injury determined by genetic and lifestyle factors.

At present, interpretation of available results remains difficult due to the variety of physiological networks involved, and differences in biomarkers and methods used as well as in nutritional composition of foods. The development of integrative panels including biomarkers together with physiological tests could help better understand the interactions of key redox responses to exercise and nutritional intake on an individual basis.

Athletes' performance is related to training and physical adaptation, and correct nutrition in individuals with specific genetic characteristics can facilitate such adjustments. Wisely, Hippocrates stated, "If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would find the safest way to health." After more than 2000 years, we are still aware that interactions between training, physiological adaptations and well-being, competition, and nutrition require an integrated and personalized approach, which should be continuously designed and adjusted to the contingent requirements of each single athlete. Thus, while awaiting new insights in this research area, dietary regimens for athletes must be developed by an expert medical staff, considering individual physiological characteristics, and intensity as well as duration of the training programs.

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References

[1] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84.
[2] Vassalle C, Pingitore A, De Giuseppe R, Vigna L, Bamonti F. Biomarkers to estimate bioefficacy of dietary/supplemental antioxidants in sports. In: Lamprecht M, editor. Antioxidants in sport nutrition. Boca Raton, FL: Taylor & Francis Group; 2015. p. 255–72.
[3] Peternelj TT, Coombes JS. Antioxidant supplementation during exercise training: Beneficial or detrimental? Sports Med 2011;41:1043–69.
[4] Brisswalter J, Louis J. Vitamin supplementation benefits in master athletes. Sports Med 2014;44:311–8.
[5] Wilkinson M, Hart A, Milan SJ, Sugumar K. Vitamins C and E for asthma and exercise-induced bronchoconstriction. Cochrane Database Syst Rev 2014;6:CD010749.
[6] Myburgh KH. Polyphenol supplementation: benefits for exercise performance or oxidative stress? Sports Med 2014;44(Suppl 1):S57–70.
[7] Milan SJ, Hart A, Wilkinson M. Vitamin C for asthma and exercise-induced bronchoconstriction. Cochrane Database Syst Rev 2013;10:CD010391.
[8] Dato S, Crocco P, D'Aquila P, de Rango F, Bellizzi D, Rose G, et al. Exploring the role of genetic variability and lifestyle in oxidative stress response for healthy aging and longevity. Int J Mol Sci 2013;14:16443–72.
[9] Morales-Alamo D, Calbet JA. Free radicals and sprint exercise in humans. Free Radic Res 2014;48:30–42.
[10] Vassalle C. An easy and reliable automated method to estimate oxidative stress in the clinical setting. Methods Mol Biol 2008;477:31–9.
[11] Bloomer RJ, Fisher-Wellman KH. Blood oxidative stress biomarkers: influence of sex, exercise training status, and dietary intake. Gend Med 2008;5:218–28.
[12] Falone S, Mirabilio A, Pennelli A, Cacchio M, Di Baldassarre A, Gallina S, et al. Differential impact of acute bout of exercise on redox- and oxidative damage-related profiles between untrained subjects and amateur runners. Physiol Res 2010;59:953–61.
[13] Vassalle C, Lubrano V, L'Abbate A, Clerico A. Determination of nitrite plus nitrate and malondialdehyde in human plasma: analytical performance and the effect of smoking and exercise. Clin Chem Lab Med 2002;40:802–9.
[14] Ortenblad N, Madsen K, Djurhuus MS. Antioxidant status and lipid peroxidation after short-term maximal exercise in trained and untrained humans. Am J Phys 1997;272:1258–63.
[15] Dékány M, Nemeskéri V, Györe I, Harbula I, Malomsoki J, Pucsok J. Antioxidant status of interval-trained athletes in various sports. Int J Sports Med 2006;27:112–6.
[16] Radak Z, Chung HY, Goto S. Systemic adaptation to oxidative challenge induced by regular exercise. Free Radic Biol Med 2008;44:153–9.
[17] Oztasan N, Taysi S, Gumustekin K, Altinkaynak K, Aktas O, Timur H, et al. Endurance training attenuates exercise-induced oxidative stress in erythrocytes in rat. Eur J Appl Physiol 2004;91:622–7.
[18] Vassalle C, Piaggi P, Weltman N, Prontera C, Garbella E, Menicucci D, et al. Innovative approach to interpret the variability of biomarkers after ultra-endurance exercise: the multifactorial analysis. Biomark Med 2014;8:881–91.
[19] Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? Med Sci Sports Exerc 2001;33:459–71.
[20] Corbi G, Conti V, Russomanno G, Rengo G, Vitulli P, Ciccarelli AL, et al. Is physical activity able to modify oxidative damage in cardiovascular aging? Oxid Med Cell Longev 2012;2012:728547.

[21] Higashida K, Kim SH, Higuchi M, Holloszy JO, Han DO. Normal adaptations to exercise despite protection against oxidative stress. Am J Physiol Endocrinol Metab 2011;301:779–84.
[22] Braakhuis AJ, Hopkins WG, Lowe TE. Effects of dietary antioxidants on training and performance in female runners. Eur J Sport Sci 2014;14:160–8.
[23] Frei B, Birlouez-Aragon I, Lykkesfeldt J. Authors' perspective: what is the optimum intake of vitamin C in humans? Crit Rev Food Sci Nutr 2012;52:815–29.
[24] Food and Nutrition Board. Institute of Medicine, Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press; 2002.
[25] Gomez Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo FV, et al. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. Am J Clin Nutr 2008;87:142–9.
[26] Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, et al. Position statement. Part two: Maintaining immune health. Exerc Immunol Rev 2011;17:64–103.
[27] Marzocchella L, Fantini M, Benvenuto M, Masuelli L, Tresoldi I, Modesti A, et al. Dietary flavonoids: molecular mechanisms of action as antiinflammatory agents. Recent Pat Inflamm Allergy Drug Discov 2011;5:200–20.
[28] Murase T, Haramizu S, Ota N, Hase T. Tea catechin ingestion combined with habitual exercise suppresses the aging-associated decline in physical performance in senescence-accelerated mice. Am J Physiol Regul Integr Comp Physiol 2008;295:281–9.
[29] Lima GPP, Vianello F. Review on the main differences between organic and conventional plant-based foods. Int J Food Sci Technol 2011;46:1–13.
[30] Gonçalves MC, Bezerra FF, Eleutherio ECA, Bouskela E, Koury J. Organic grape juice intake improves functional capillary density and postocclusive reactive hyperemia in triathletes. Clinics 2011;66:1537–41.
[31] Olholm J, Paulsen SK, Cullberg KB, Richelsen B, Pedersen SB. Antiinflammatory effect of resveratrol on adipokine expression and secretion in human adipose tissue explants. Int J Obes [Lond] 2010;34:1546–53.
[32] Boutant M, Cantó C. SIRT1 metabolic actions: integrating recent advances from mouse models. Mol Metab 2013;3:5–18.
[33] Davis JM, Murphy EA, Carmichael MD, Davis B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 2009;296:1071–7.
[34] González-Gallego J, García-Mediavilla MV, Sánchez-Campos S, Tuñón MJ. Fruit polyphenols, immunity and inflammation. Br J Nutr 2010;104:15–27.
[35] Davis JM, Carlstedt CJ, Chen S, Carmichael MD, Murphy EA. The dietary flavonoid quercetin increases VO[2 max] and endurance capacity. Int J Sport Nutr Exerc Metab 2010;20:56–62.
[36] Nieman DC, Henson DA, Davis JM, Dumke CL, Gross SJ, Jenkins DP, et al. Quercetin ingestion does not alter cytokine changes in athletes competing in the Western States Endurance Run. J Interferon Cytokine Res 2007;27:1003–11.
[37] Nieman DC, Henson DA, Gross SJ, Jenkins DP, Davis JM, Murphy EA, et al. Quercetin reduces illness but not immune perturbations after intensive exercise. Med Sci Sports Exerc 2007;39:1561–9.
[38] Kressler J, Millard-Stafford M, Warren GL. Quercetin and endurance exercise capacity: a systematic review and meta-analysis. Med Sci Sports Exerc 2011;43:2396–404.
[39] Henriksen EJ. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. Free Radic Biol Med 2006;40:3–12.
[40] Ghibu S, Richard C, Vergely C, Zeller M, Cottin Y, Rochette L. Antioxidant properties of an endogenous thiol: alpha-lipoic acid, useful in the prevention of cardiovascular diseases. J Cardiovasc Pharmacol 2009;54:391–8.
[41] Zembron-Lacny A, Gajewski M, Naczk M, Dziewiecka H, Siatkowski I. Physical activity and alpha-lipoic acid modulate inflammatory response through changes in thiol redox status. J Physiol Biochem 2013;69:397–404.
[42] Lass A, Sohal RS. Effect of coenzyme Q_{10} and α-tocopherol content of mitochndria on the production of superoxide anion radicals. FASEB J 2000;14:87–94.
[43] Weber C, Jakobsen TS, Mortensen SA, Paulsen G, Hølmer G. Antioxidative effect of dietary coenzyme Q_{10} in human blood plasma. Int J Vitam Nutr Res 1994;64:311–5.
[44] Díaz-Castro J, Guisado R, Kajarabille N, García C, Guisado IM, de Teresa C, et al. Coenzyme Q[10] supplementation ameliorates inflammatory signaling and oxidative stress associated with strenuous exercise. Eur J Nutr 2012;51:791–9.
[45] Ostman B, Sjödin A, Michaëlsson K, Byberg L. Coenzyme Q10 supplementation and exercise-induced oxidative stress in humans. Nutrition 2012;28:403–17.
[46] Nieman DC, Henson DA, McAnulty SR, Jin F, Maxwell KR. n-3 polyunsaturated fatty acids do not alter immune and inflammation measures in endurance athletes. Int J Sport Nutr Exerc Metab 2009;19:536–46.
[47] Mickleborough TD. Omega-3 polyunsaturated fatty acids in physical performance optimization. Int J Sport Nutr Exerc Metab 2013;23:83–96.
[48] Wang X, Quinn PJ. Vitamin E and its function in membranes. Prog Lipid Res 1999;38:309–36.
[49] Stepanyan V, Crowe M, Haleagrahara N, Bowden B. Effects of vitamin E supplementation on exercise-induced oxidative stress: a meta-analysis. Appl Physiol Nutr Metab 2014;39:1029–37.
[50] Venditti P, Napolitano G, Barone D, Di Meo S. Effect of training and vitamin E administration on rat liver oxidative metabolism. Free Radic Res 2014;48:322–32.
[51] Tomasello B, Grasso S, Malfa G, Stella S, Favetta M, Renis M. Double-face activity of resveratrol in voluntary runners: assessment of DNA damage by comet assay. J Med Food 2012;15:441–7.
[52] McGinley C, Shafat A, Donnelly AE. Does antioxidant vitamin supplementation protect against muscle damage? Sports Med 2009;39:1011–32.
[53] Diel F, Khanferyan RA. Standards of nutrition for athletes in Germany. Vopr Pitan 2013;82:14–8.
[54] Jeukendrup A. A step toward personalized sports nutrition: carbohydrate intake during exercise. Sports Med 2014;44:25–33.
[55] Pérez-López FR, Chedraui P, Haya J, Cuadros JL. Effects of the Mediterranean diet on longevity and age-related morbid conditions. Maturitas 2009;64:67–79.
[56] Leighton F, Cuevas A, Guasch V, Pérez DD, Strobel P, San Martín A, et al. Plasma polyphenols and antioxidants, oxidative DNA damage and endothelial function in a diet and wine intervention study in humans. Drugs Exp Clin Res 1999;25:133–41.
[57] Fitó M, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, et al, PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch Intern Med 2007;167:1195–203.
[58] Urquiaga I, Strobel P, Perez D, Martinez C, Cuevas A, Castillo O, et al. Mediterranean diet and red wine protect against oxidative damage in young volunteers. Atherosclerosis 2010;211:694–9.
[59] Fernández JM, Rosado-Álvarez D, Da Silva Grigoletto ME, Rangel-Zúñiga OA, Landaeta-Díaz LL, Caballero-Villarraso J, et al. Moderate-to-high-intensity training and a hypocaloric Mediterranean diet enhance endothelial progenitor cells and fitness in subjects with the metabolic syndrome. Clin Sci 2012;123:361–73.
[60] Landaeta-Díaz L, Fernández JM, Da Silva-Grigoletto M, Rosado-Alvarez D, Gómez-Garduño A, Gómez-Delgado F, et al. Mediterranean diet, moderate-to-high intensity training, and health-related quality of life in adults with metabolic syndrome. Eur J Prev Cardiol 2013;20:555–64.
[61] Toro R, Mangas A, Quezada M, Rodriguez-Rosety M, Fournielles G, Rodriguez-Rosety I, et al. Diet and exercise influence on the proteomic profile of an athlete population. Nutr Hosp 2014;30:1110–7.